

9. (Currently Amended) A method of treatment for necrotizing enterocolitis, comprising:

a) providing:

- i) a neonate at risk for necrotizing enterocolitis,
- ii) a therapeutic formulation comprising anti-TNF polyclonal antibody ~~directed to TNF~~, and;

b) administering said formulation to the lumen of the intestine of said neonate.

10. (Previously Presented) The method of Claim 9, wherein said neonate is a low birth weight neonate.

11. (Previously Presented) The method of Claim 9, wherein said administering reduces said symptoms.

12. (Previously Presented) The method of Claim 9, wherein said administering is performed orally.

13. (Previously Presented) The method of Claim 9, wherein said administering is performed parenterally.

14. (Previously Presented) The method of Claim 9, wherein said administering is performed rectally.

### **R E M A R K S**

Claims 1-14 are pending. The Examiner has offered the following grounds of rejection:

Claims 1-14 are rejected under 35 U.S.C. 103(a) as allegedly obvious in light of Eible ('984 patent) or Lai ('532 patent) in view of Mugurum *et al.*, Eibl (Acta Pediat) and further in view of Emery *et al.* (US Patent No. 5,420,253).

**The Claims Are Not Obvious**

Claims 1-14 are rejected under 35 U.S.C. 103(a) as allegedly obvious in light of Eible ('984 patent) or Lai ('532 patent) in view of Mugurum *et al.*, Eibl (Acta Pediatr) and further in view of Emery *et al.* (US Patent No. 5,420,253). Applicants respectfully disagree.

The Examiner insists that the claims do not have the element of anti-TNF antibodies, merely "antibodies directed to TNF." While not agreeing with the Examiner,<sup>1</sup> but to the further the prosecution, the independent claims have been amended to specifically require anti-TNF antibodies. With this amendment, Applicant's arguments are NOT moot and are repeated here for the Examiner's convenience:

**A. The References Do Not Teach The Elements Claimed**

a. The Examiner has previously admitted that "Eibl fails to specifically use anti-TNF antibodies in treating NEC."

b. The authors of the '984 patent implicitly rule out direct antibody inhibition of the cytokine.

c. The IgA described in the '984 patent was simply prepared by plasma fractionation - not by using TNF as an antigen.

d. There is no evidence that such human plasma IgA of the '984 patent reacts with TNF.

e. The Examiner has admitted that "Lai . . . does not disclose administration of anti-TNF antibodies to human neonates."

f. Lai warns that therapeutic methods utilizing anti-TNF antibodies "have met with only limited success."

g. The Wolf (Acta Pediatr. Suppl) teaches only the use of IGABULIN (see page 38, right column, bottom). This is not an anti-TNF antibody.

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<sup>1</sup> The Examiner is not free to ignore the plain meaning of claim terms. The clear meaning of "antibodies directed to TNF" (when read in the context of the specification - as law requires the Examiner to do) is that the antibodies were raised against TNF as an antigen, thereby producing antibodies with specificity for TNF.

**B. The Proper Standards For A 103 Rejection Have Not Been Used**

To establish *prima facie* obviousness, the Examiner must point to some motivation or suggestion within the references themselves, or within the knowledge generally available to one of ordinary skill in the art at the time of invention, to combine or modify the references. See MPEP §2143.01; *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988). Merely because the references *could be* combined or modified does not render the resultant combination obvious unless the prior art suggested the combination. MPEP §2143.01; *In re Mills*, 916 F.2d 680, 682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990).

The Examiner concludes that "it would be obvious to one of ordinary skill in the art at the time of invention to employ such antibodies . . ." (Office Action, p. 4). The Examiner's only support offered for the conclusion is simply the general teachings that TNF is a "pro-inflammatory mediator in development of necrotic enterocolitis." (Office Action, p. 4).

Applicant submits this is not adequate support for an obviousness rejection of claims that specify a particular mode of treatment, *i.e.* polyclonal antibodies administered to the lumen of the intestine of the subject. First, the law does not regard the Examiner as one skilled in the art. See *In re Rijckaert*, 28 USPQ2d 1955 at 1956 (Fed. Cir. 1993)("[T]he examiner's assumptions do not constitute the disclosure of the prior art."); See *id.* at 1957 ("[W]hen the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears."). Second, the Federal Circuit has made it clear that "[b]road, conclusory statements regarding the teachings of multiple references, standing alone, are not 'evidence.'" *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614 (Fed. Cir. 1999).

**C. The References Cannot Be Considered Collectively**

Applicants submit that the references cannot be considered collectively until the Examiner points to some *evidence* to support combining those references. The purpose behind this requirement is to prevent the Examiner from using the invention itself and hindsight reconstruction to defeat the patentability of the invention. The Federal Circuit, in a recent decision, articulates this position:

To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the

inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

*See In re Rouffet et al.*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998).

The Examiner's Office Action does not address this point. The Examiner does not mention the *Rouffet* case. Rather, the Examiner cites the *Keller* and *Merck* cases for the proposition that one cannot attack the references individually. However, neither case supports ignoring the threshold requirement of providing evidence to support the combination in the first instance (moreover, the *Keller* case relies on pre-*Graham* cases for the point)

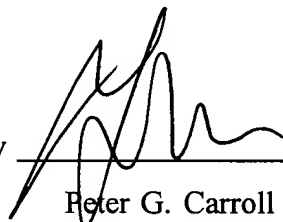
### CONCLUSION

Applicants believe that the arguments set forth above traverse the Examiner's rejections and therefore request that these grounds for rejection be withdrawn for the reasons set forth above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (617)-252-3353.

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